Attorney Docket # 4948-2PRCE3

Patent

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of

Carlos PICORNELL DARDER

Serial No.: 09/491,624

Filed: January 26, 2000

For: Oral Pharmaceutical Preparation Comprising an Antiulcer Activity Compound, and Process for its Production

Examiner: Sharmila S. Gollamudi
Group Art: 1616

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December 21, 2007
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## APPEAL BRIEF

SIR:

This is an appeal, pursuant to 37 C.F.R. § 41.37 from the decision of the Examiner in the above-identified application, as set forth in the Final Office Action of July 27, 2007 wherein the Examiner finally rejected Appellant's claims. The rejected claims are reproduced in the Appendix A attached hereto. A Notice of Appeal was filed on October 29, 2007.

The fee of $255.00 for filing an Appeal Brief pursuant to 37 C.F.R. § 41.20 is submitted herewith. Any additional fees or charges in connection with this application may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

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## REAL PARTY IN INTEREST

The assignee[1], Liconsa, Liberación Controlada de Sustancias Activas, S.A. is the real party of interest in the above-identified U.S. Patent Application.

## RELATED APPEALS AND INTERFERENCES

There are no other appeals and/or interferences related to the above-identified application at the present time.

## STATUS OF CLAIMS

Claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-50 were finally rejected. Claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-50 are on appeal.

## STATUS OF AMENDMENTS

An Amendment After Final Rejection was filed on September 27, 2007 in response to the Final Office Action. The Examiner issued an Advisory Action in reply on October 16, 2007 refusing to enter that Amendment and maintaining the rejections of July 27, 2007.

## SUMMARY OF THE CLAIMED SUBJECT MATTER

### Independent claim 34

Independent Claim 34 relates to a process for making an oral pharmaceutical preparation. (Specification, page 15, lines 3 to 18). The process comprises coating an inert nucleus to form a substantially non-porous layer thereon by spraying on the nucleus an aqueous or hydroalcoholic suspension solution. The sprayed solution comprises an active ingredient which active ingredient is a compound having anti-ulcer activity. (Specification, page 8, lines 15 to 21). The active ingredient is a substituted benzimidazole compound. (Specification, page 7, line 6 to

[1] The assignee of record has changed its name to Laboratories Liconsa, S.A.

page 8, line 14). The aqueous or hydroalcoholic suspension solution also comprises an alkaline reacting compound and at least one pharmaceutically acceptable excipient which can be a binder, and/or a surface active agent and/or a filling material and/or a disintegrating swelling excipient. (Specification, page 11, line 1 to page 12, line 15). The active layer which is formed during the spraying is then dried to form a charged nucleus (Specification, page 16, lines 17 to 19). The charged nucleus is coated by spraying on the charged nucleus, a solution which contains an enteric coating polymer on the charged nucleus so as to form a gastro-resistant external coating. (Specification, page 16, line 10 to page 18, line 4). Each of the steps of the coating of the inert nucleus, the drying of the active layer to form the charged nucleus and the coating of the charged nucleus are performed in a Wurster-type fluidized bed coater. (Specification, page 17, lines 17 to 20).

**Independent Claim 36**

Independent claim 36 is drawn to a process for making an oral pharmaceutical preparation which again comprises coating an inert nucleus in a fluidized bed coater to form a substantially non-porous layer thereon by spraying on the nucleus an aqueous or hydroalcoholic suspension solution. The suspension solution includes an active ingredient, which is an anti-ulcer compound of the specified formulae, an alkaline reacting compound and a pharmaceutically acceptable excipient. The active layer that is formed on the inert nucleus is dried to form a charged nucleus in the fluid bed coater and the charged nucleus is coated in the fluid bed coater by spraying on the charged nucleus a solution containing an enteric coating polymer with at least one pharmaceutically acceptable excipient to form a gastro-resistant external coating layer thereon.

(Specification, page 15, lines 3 to 18). The fluidized bed coater is a Wurster-type fluidized bed coater. (Specification, page 17, lines 18 to 20).

**GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

1. The rejection of claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-46 and 49 under 35 U.S.C. § 103(c) as unpatentable over U.S. Patent No. 6,365,184 to DePui et al. ("DePui '184") by itself or in view of Wurster, U.S. Patent No. 2,799,241 ("Wurster").

2. The rejection of claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-46 and 49 under 35 U.S.C. §103(c) as unpatentable over U.S. Patent No. 6,132,771 to DePui et. al. ("DePui '771") in view of Ohno et al., U.S. Patent No. 4,017,647 ("Ohno") or Wurster.

3. The rejection of claims 15, 16, 18-25, 30, 31, 33, 34, 39-46 and 49 under 35 U.S.C. §103(a) as unpatentable over WO 96/01624 ("WO '624") in view of Ohno or Wurster.

4. The rejection of claims 47, 48 and 50 under 35 USC §103(a) as unpatentable over DePui '184 in view of Wurster in view of U.S. Patent No. 5,232,706 to Palomo Coll ("Palomo") further in view of U.S. Patent No. 5,219,879 to Kim et. al. ("Kim").

5. The rejection of claims 47, 48 and 50 under 35 U.S.C. 103(a) as unpatentable over DePui '771 or WO '624 respectively, in view of Ohno or Wurster respectively, in view of Palomo or Kim.

**ARGUMENT**

Since each of the Grounds of Rejection to be reviewed on Appeal relies on one or more of the DePui '184, DePui '771 or WO '624, which are all substantially similar in their disclosures as the primary reference, Grounds 1 to 5 will be addressed collectively.

## Background of the Invention

The invention defined by the now pending claims is for a process of producing a pharmaceutical preparation of an active ingredient which is an anti-ulcer compound, i.e., a proton pump inhibitor ("PPI") of the class of compounds known as substituted benzimidazoles. Such compounds are known to be acid labile and degrade rapidly when exposed to an acidic environment. When such compounds are exposed to the gastric environment[2], they can rapidly degrade within the stomach. This is not desirable. Enteric coatings, used to protect a dosage form from stomach acid, are also acidic thus causing premature degradation of the benzimidazole.

Another technique, to include an alkaline substance with the active ingredient to protect the active, caused the enteric coating, by chemical interaction, to break down thus exposing the active ingredient to stomach acid resulting in a rapid degradation of the active ingredient. On the other hand, the body must be able to process the dosage form so that it is able to deliver the active ingredient to the parietal cell in the mucosal lining of the stomach where the proton pump inhibitors are activated. The dosage form cannot be so impervious that it does not release the active ingredient at the proper time.

Lovgren proposed the solution of including a water soluble or rapidly disintegrating separating layer to separate the active ingredient and alkaline material from the enteric coating. See U.S. Patent Nos. 4,786,505 ("the '505 Patent") and 4,853,230 (the '230 Patent") to Lovgren et al. This structural barrier separates and protects the enteric coating from the alkaline compounds needed to protect the active ingredient. The result is that the

[2] Gastric juice contains hydrochloric acid and is estimated to be at a pH of about 1.

pharmaceutical composition is safe from the stomach acid. The active ingredient is released in an environment that does not result in the active ingredient being degraded.

Independent claims 34 and 36 are directed to a process for forming a pharmaceutical composition for oral administration. As defined above under the Summary of the Claimed Subject Matter, the claims recite processes wherein an inert nucleus is coated with a substantially non-porous layer that has been applied by spraying onto that nucleus an aqueous or hydroalcoholic suspension solution. The sprayed solution comprises the active ingredient, which is an anti-ulcer compound of the substituted benzimidazole type, and including an alkaline reacting compound and at least one pharmaceutically acceptable excipient. The coated nucleus is dried and coated with a solution which contains an enteric coating polymer which forms a gastro-resistant external coating of the pharmaceutical composition. The steps are carried out in a Wurster-type fluidized bed coater.

**B. Art Relied Upon for the Final Rejection**

The art relied upon by the Examiner is as follows:

| Patentee | Patent No. |
|---|---|
| DePui et al. | 6,365,184 |
| DePui et al. | 6,132,771 |
| Wurster | 2,799,241 |
| Ohno et al. | 4,017,647 |
| Kim et al. | 5,219,879 |
| WIPO | WO 96/01624 |

**DePui '771**

DePui '771, assigned to Astra-Zeneca, is directed to oral pharmaceutical dosage forms for a combined therapy against GORD (Gastro Oesophageal Reflux Disease). The dosage forms are tablets containing an acid suppressing agent (proton pump inhibitors i.e. omeprazole,

lansoprazol, pantoprazole..) and a prokinetic agent (i.e. cisapride, mosapride,...). In DePui 771, the formed benzimidazole containing pellets are intermixed with a mixture containing tablet excipients and a prokinetic agent. That resulting mixture is then subjected to tabletting operations and is coated with an external enteric coating. Thus, the pellets are separated from the dosage form external coating by tablet excipients as well as the second active ingredient.

DePui '771 describes as "obvious" that the proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer and specifically refers to Lovgren's U.S. Patent No. 4,786,505 ("the 505 Patent")[3] for omeprazole preparations (see col. 2, lines 50-57) for a description of enteric coating layered preparations of proton pump inhibitors. The '505 Patent discloses a formulation wherein the active containing region of the dosage form is separated from the external enteric coating by one or more intermediate layers.

The objective of DePui is to obtain an oral multi-unit tablet dosage form simultaneously containing both an acid suppressive agent and a prokinetic agent wherein the enteric coating of the imbedded pellets is not adversely affected in the compression tabletting operation to form the dosage form. DePui '771 discloses a dosage form that addresses a mechanical problem affecting dosage forms which are subjected to a tabletting process which DePui suggests had in the past mechanically weakened enteric coatings rendering the film coatings susceptible to failure allowing gastric juice to attack the active. DePui '771 is not directed to chemical incompatabilities in pharmaceutical compositions of an enteric coated

[3] The '505 patent has been successfully asserted by one or more companies related to Astra-Zeneca against numerous generic companies seeking to market generic omeprazole pharmaceutical preparations.

preparation of a proton pump inhibitor. DePui had referred to Lovgren '505 to address that consideration.

All 14 examples of DePui '771 refer to, or describe, a composition which, with respect to the proton pump inhibitor, have, an alkaline substance, at least one separating layer between the core and the surrounding enteric coating and an over-coating. The alkaline substance can be included as a basic salt of the corresponding proton pump inhibitor, i.e. omeprazole magnesium salt[4], as stated in the '505 (col. 4, lines 23 to 27) and '230 (col. 8, lines 55 to 61) patents. There is not a single example or suggestion in DePui '771 of how to produce a stable and useful composition as defined in the presently pending claims.

**2. DePui '184**

The disclosure of DePui '184 is substantially similar to that of DePui '771 but the second active ingredient is a non-steroidal anti-inflammatory agent ("NSAID") in place of the prokinetic agent. DePui '184 also refers to Lovgren '505 to protect the proton pump inhibitors. See col. 2, lines 41 to 50.

In each of the examples of the DePui '184 invention, the dosage form is formed with an alkaline material and both a separating layer between the benzimidazole and the enteric coating and an over-coating layer covering the enteric coated benzimidazole pellets. DePui '184 refers to Examples 5, 7 and 10 each of which have both the separating layer and over-coating as the best mode of practicing the invention (col. 24, lines 33 to 35). The above comments regarding DePui '771 are equally applicable to DePui '184.

[4] An optical isomer of the magnesium salt of omeprazole is the active ingredient in Astra's Nexium® product.

## WO '624

According to German Patent Office Records, U.S. Patent No. 5,753,265 corresponds to this document.

WO '624 discloses a multiple unit dosage form for oral administration in the form of a tablet wherein pellets of a proton pump inhibitor are embodied in the dosage form. Here again the concern is with the integrity of the enteric coating of the embedded pellets after compression tabletting processes. WO '624 also uses over-coating techniques.

In each of the WO '624 examples a tablet dosage form is produced using active pellets which are enteric coated then mixed with microcrystalline cellulose and tabletting agent(s). Each of Examples 1 to 10 and 12 to 16 unequivocally states that the pellet compositions are formed with an intermediate separating layer keeping the active benzimidazole separate from the enteric coating. In each of Examples 1 and 10, the active coated pellets are mixed with tablet excipients and formed into tablets by compression. Example 11 of WO '624 uses a core composition according to Example 1 or Example 10 thereof but does not mention use of a separating layer within the pellet. The pellets are admixed with tabletting excipients. WO '624 at page 32 reports acid resistance for Examples 1 and 10 but not for Example 11. At page 35, acid resistances for prior art layered pellets are reported to be well over 95% but the tablets without the over-coating do not perform as well.

### 4. Wurster

Wurster discloses methods and apparatus for applying coatings and in particular, applying coatings to medicinal tablets, chewing gum, candies and nuts.

### 5. Palomo Coll

Palomo relates to a dosage form of omeprazole having an intermediate separating layer between the active region and the enteric coating and using basic compounds in the formulation.

### 6. Kim

This reference discloses an omeprazole containing dosage form for rectal administration using high weight polyethylene glycols, or a mixture of adeps solidus and sodium lauryl sulfate and water soluble basic amino acids. Kim would not be looked to by one of ordinary skill since the problem for the present invention is not encountered in the dosage forms to which Kim is addressed. The reference does acknowledge the problem of rapid degradation of the proton pump inhibitor compounds. See col. 1, lines 14 to 30.

## C. The Claimed Subject Matter is Not Obvious From the Cited Art

### 1. There is no *Prima-Facie* Case of Obviousness

#### a) *The DePui References Fail on Their Face to Disclose and Enable the Now Claimed Invention*

The rejection of the claims based on either of the DePui references alone or in combination with any of the other cited references is premised on DePui's use of the word "optional" with respect to the use of a separating layer in the dosage forms disclosed and claimed in each of those references. The rejection, ignoring the fact that the dosage forms disclosed in each of those references are made up of additional components, structures and processing, erroneously and improperly mutates the word "optional" into an enabling disclosure of a different pharmaceutical

composition violating a fundamental principle underlying 35 USC §103. The rejections are also premised on fundamental procedural errors which will be discussed below.

Rather than properly address issues repeatedly raised by Applicant so as to focus the issues, the Office Actions, became more and more speculative as Applicant attempted to address and explain what, appeared from the Office Actions, to be fundamental misunderstandings.

The disclosure of DePui '184, which is largely duplicative of the disclosure in DePui '771, has been discussed extensively above. Neither of DePui '184 or DePui '771 are focused on process technology and what information is provided regarding the process or processes used in those references is at best superficial.

With respect to process considerations, it appears the rejection's only comment different from DePui '771 is in reference to Example 4 of DePui '184. However, neither that example nor any other disclosure in DePui '184 suggests the now claimed subject matter.

It is clear from the wording of DePui '184 Example 4 that there are at least two separate operational apparatus employed with respect to the production of pellets in that example. Further, the example is directed to providing a multi-active containing tablet. It is undisputed that in Example 4 there is a separating layer applied on to the suspension layered core within the pellet. Subsequently, an enteric coating is applied on the separating layer to form the enteric coated pellets. Further, these enteric coated pellets are then mixed in a granulated and dried mix of an NSAID (Naproxen®) and other materials in tablet compression steps to form a pharmaceutical composition of the Example. This is in direct contrast to the present claim language wherein the enteric coating solution is sprayed to form a gastro-resistant external coating layer on the charged nucleus i.e., no

intermediate layer. DePui '184 fails to suggest that the nucleus is formed with a substantially non-porous active containing layer as is clearly recited in the presently pending claims.

To support the rejection the Examiner, in effect, rewrote Example 4 as if the production of the pellet were the end product dosage form of DePui's invention or even of that example. That is not permissible and a flagrant violation of 35 USC §103 requiring that the art be considered as a whole.

The Final Rejection does not 1) dispute that the pellets of Example 4 each contain a separating layer and 2) that there is no example of a dosage form with pellets without a separating layer in DePui '184. The Final Rejection further does not dispute the failure of not only Example 4, but the failure of the entire reference, to suggest the seed is coated with a substantially non-porous active containing layer. The Final Rejection does not dispute that DePui '771 does not disclose applying a substantially non-porous active containing layer to a nucleus and that none of the examples show pellets without a separating layer.

Neither of the DePui references or WO '624 discloses a pharmaceutical composition showing or suggesting a substantially non-porous layer containing the active ingredient, and that such a layer is coated with an enteric coating which forms a gastro-resistant external coating layer on the charged nucleus. Additionally, neither of the DePui references or WO '624 shows or suggests performing the process in a Wurster-type fluidized bed. None of the other references remedy these fundamental deficiencies of both the DePui references and WO '624. Thus, there is no basis for a conclusion of obviousness based on either of the DePui references or WO '624 alone or in combination with the other cited references.

It is clear from the disclosures of DePui '184, DePui '771 and WO '624 that the problems which those references seek to address in both the product, and process for making that product, are those which arise in a single fixed unit dosage form containing multiple active substances that have different physical, chemical and pharmacological properties in the course of forming tablets by compression techniques. According to the references, preparation of multiple unit dosage forms gives rise to specific problems not encountered in a single active dosage form. See DePui '184 at col. 2, ll. 51 to 63.

The DePui references and WO '624 fail to describe how a stable and useful oral form of a proton pump inhibitor ("PPI") dosage composition can be made without having both an alkaline reacting substance and at least one separating layer or region between the region containing the PPI and the external enteric coating. That is to say, assuming that DePui or WO '624 ever contained sufficient disclosure to identify such a composition (which is disputed), each fails to contain enabling disclosure as to how to make such a composition.

Further, there is no basis to believe that DePui's or any of the WO '624 formulations are stable. Such information cannot be assumed. Applicant repeatedly called upon the Examiner to comply with the requirements of 37 CFR §1.104(d)(2) on this point but that was also ignored.

The Final Rejection refers to column 9, lines 46-50 and column 10, lines 41 to 43, of each of DePui '184 and DePui '771 and maintains that the reference discloses "the optionally applied separating layer is not essential for the invention". However ,such phraseology does not amount to a disclosure of how to make such an embodiment not only in DePui's invention but in other pharmaceutical compositions and is remote from the issues at hand. Whether the separating layer is optional in the pharmaceutical composition of DePui '184 or DePui '771, i.e., a multi-unit tablet

dosage form, has no relevance to the present issues. DePui and WO '624 seek to protect the mechanical integrity of the enteric coating in the pellets which are mixed with another active and/or tabletting excipients sometimes with an over-coating in a compression tabletting process.

As can be understood from the above discussion of WO '624 (also owned by Astra), there is little difference between that reference and the DePui references. The Examiner cited to Example 11 of the WO '624 reference and this has been discussed above. As in DePui, the enteric coating pellets are further treated with tablet excipients and subjected to further processing.

The present invention proceeded opposite to the prior art teachings and removed a structural element, i.e., a separating layer from the dosage form when the prior art (Lovgren '505) taught this structural element was necessary for chemical protection of the active ingredient. Thus, not only do the DePui and WO '624 references address a different problem but, because of the over-coating or tablet excipients covering the enteric coating, do not have the same problem addressed by the present invention. Thus, one would not look to these references.

The Final Rejection asserts that Wurster teaches that a Wurster-type fluidized apparatus provides a uniform coating preventing a coating material from sticking to the inner surface of the chamber.

Applicants do not deny that a Wurster-type fluidized apparatus was known and was used for coating. While Wurster mentions tablets, chewing gum, candies and nuts, the reference does not mention pellet cores. Further, what is not disclosed or suggested in any of the references is that this type of apparatus can be operated so as to obtain a substantially non-porous soluble active layer which can eliminate the need for a separating layer in those types of formulations where the prior art required the presence of the separating layer to protect the active ingredient from the

deleterious affects of enteric coatings. None of the cited art provides a disclosure or suggestion of such a feature or how to obtain it. See *Ex parte Wisdom & Hilton*, 184 USPQ 822, 823 (POBA 1973) (process claim not obvious based on reference which doesn't recognize problem solved by Applicant). None of the art recognized or suggested that the application of the substantially non-porous active layer would solve the problem because the source of the problem was believed to be the migration of acidic ions from the enteric coating into the active containing region.

The Final Rejection refers to Ohno as teaching a method for providing an enteric coating on solid dosage forms. The objective of the Ohno disclosure is to enteric coat a dosage form with an aqueous solution of a polymeric substance having carboxyl groups as a water soluble salt and contacting the coated dosage form with an inorganic acid to covert the polymer substance into the water insoluble acid form. Unfortunately, the Final Rejection misstates the disclosure of Ohno. Col. 3, ll. 24 to 40 of Ohno is cited as support for application of Ohno as a reference. However, no where in the Ohno reference is there a disclosure that coating apparatus such as pan coaters, drum-type coaters, or Wurster-type fluidized coaters...are equivalent or the same or operate under the same principle. Rather, Ohno discloses that once someone selects a type of coating apparatus, one can use the same conditions of operation for that particular apparatus in applying either an aqueous-based coating material or an organic solvent based coating material. More specifically, Ohno states:

> There is no difference in principle between the conditions with which the solid dosage forms are coated in accordance with the invention and those with which the aforementioned conventional coaters are operated using a coating solution with an organic solvent.

Thus, the very basis on which the Final Rejection relies for the citation or combination of Ohno in the rejection is in error. Ohno does not provide a broad teaching of equivalency or suggest that the results obtained by all coating apparatus are equivalent. Any one in the art would know that this is simply not true.[5] It is not permissible to modify the disclosure of a reference so as to suggest that which the actual text does not, *In re Hummer,* 241 F.2d 742, 113 USPQ 66 at 69 (CCPA 1957).

The citation of Ohno highlights that the prior art did not appreciate the significance of the procedure by which the layer is applied. See *Ex parte Wisdom & Hilton, supra.*

Palomo discloses a dosage form for omeprazole which follows the teachings of Lovgren '505 in that the dosage form therein has an intermediate coating between the drug containing region of the dosage form and the outer enteric coating. This reference adds nothing beyond the art already cited and considered. It merely identifies certain additional substances which can be used as basic compounds. However, such compounds were also suggested in Lovgren '505.

The Kim reference discloses a stabilized composition for omeprazole containing a dosage form in the form of a suppository. Neither Kim nor Palomo remedy the deficiencies of the primary references. However, Kim does confirm that the change of color is an indication of degradation for omeprazole type compounds. See the discussion at Column 1 under Background of the Invention.

It is submitted that there is no motivation established on the record to make the combination of references as has the Examiner. Clearly, those combinations are the product of

[5] The first Molina declaration (discussed below) shows that you do not obtain satisfactory results from all coaters.

hindsight reconstruction which is improper. See *In re Grabiak*, 769 F.2d 729, 226 USPQ 870, 872, (Fed. Cir. 1985).

***b) The Examiner Ignored Prior Art and Evidence Showing the Error of the Rejections.***

Applicant made a of record substantial evidence traversing the rejections but that evidence was never properly considered. That evidence included citations to prior art patents and three (3) declarations.

**1. <u>Prior Art Patents</u>**

During numerous interviews and in numerous submissions, the Lovgren '505[6] patent, which is acknowledged in the DePui references in column 2, lines 47 to 50, was discussed. Lovgren '505 is evidence showing that in the prior art a proton pump inhibitor dosage form without a separating layer, resulted in an unstable dosage form which rapidly underwent degradation. This evidence was ignored.

Attention is invited to Tables 1 to 3 of Lovgren '505. Table 1 of the '505 Patent shows core compositions 1-7 and Table 2 shows formulations I-IV for coatings for separating layers and enteric coatings for those core compositions. However, the I formulations do <u>not</u> contain an inner or outer separating layer but do contain an enteric coating layer. Table 3 shows the stability of each of the formulations as a function of the different coating techniques which are listed left-hand most of the Table 3, i.e., Roman numerals I through IV. All of the core compositions 1 through 7, which were not coated with a separating layer before application of the enteric coating, showed some degree of deterioration within seven (7) days. In that 7 day period, some of the compositions showed a substantial degree of deterioration starting as white but turning brown. Even the core

[6] Lovgren '505 and '230 have a common assignee with the DePui '184 and '771 Patents and WO '624.

materials that were treated with a coating formulation in accordance with Roman numeral II, in some instances, also showed signs of deterioration within seven days. Since both DePui '184 and DePui '771 specifically reference the Lovgren '505 patent, one of ordinary skill would have expected DePui '184 and DePui '771 to contain disclosure as to how to make a stable dosage form without a separating layer and provide an enabling disclosure as to that embodiment if the patentee had any knowledge of how to do so. However, the best that was offered in any of the Office Actions and Final Rejection with respect to either of DePui '184 or DePui '771 is that they refer to the use of the separating layer as an option.

It is submitted that where the art was aware that a separating layer was needed in pellet dosage forms, the DePui '184 and DePui '771 statements that a separating layer is not essential in a different dosage form cannot be considered as providing an enabling disclosure or realistic suggestion since reference provides absolutely no discussion or disclosure as to how to proceed to make a stable dosage form without the separating layer. As earlier indicated, there is not one single example or disclosure in either of DePui '184 or DePui '771 relating to the dosage forms that teach how to proceed without a separating layer to obtain a stable PPI dosage form of the type now claimed. Neither of DePui '184 or DePui '771 meet an obvious to try standard. Lovgren '505 and '230 dispels any reasonable expectation of success. These comments also apply to WO '624.

Even though Applicant a number of times raised the issue that the '505 Patent teaches contrary to what the DePui '771 or '184 patent is being interpreted as disclosing or suggesting, those concerns were essentially ignored and this important evidence was not considered. Rather, the Examiner took the position that since the rejection was not founded on Lovgren '505,

that patent need not be considered or addressed[7]. This is in direct contradiction to *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785, (Fed. Cir. 1984). *Piasecki* is specifically referred to in MPEP 716.01(d) as containing a detailed discussion of the proper roles with respect to a *prima facie* case[8] of obviousness and an Applicant's rebuttal evidence in the final determination of obviousness. In *Piasecki*, at page 788, the Court cited to *In re Rinehart*:

> When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over.*** An earlier decision should not, as it was here, be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability. Analytical fixation on an earlier decision can tend to provide that decision with an undeservedly broadened umbrella effect. Prima facie obviousness is a legal conclusion, not a fact. Facts established by rebuttal evidence ***must be evaluated*** along with the facts on which the earlier conclusion was reached, not against the conclusion itself.***[A] final finding of obviousness may of course be reached, but such finding will rest upon evaluation of all facts in evidence, uninfluenced by any earlier conclusion reached by an earlier board upon a different record.
> (Emphasis added)

In the present matter, Lovgren '505 and Lovgren '230 (and the Molina declaration, the Johansson declaration and the Molina-Millián declaration[9]) have not been accorded the proper weight in accordance with *Piasecki* or *Rinehart*. That is, the disclosures of DePui '184, DePui '771 or WO '624 have not been evaluated in light of any of prior art evidence acknowledged not only by the very same references relied on by the Examiner but previously relied on by the Examiner herself. Rather the rejections were treated as if set in stone while contrary evidence or art was deflected or ignored. Had there been an adherence to the law and a true reconsideration of the

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[7] This also violates 35 U.S.C. 103 requiring the art be considered as a whole and is aggravated by the fact that early in the prosecution Lovgren '505, or a foreign counterpart, was cited against the claims.
[8] As explained above, Applicant herein disputes that the Examiner ever established a *prima facie* case of obviousness.
[9] These declarations will be discussed below

rejections in view of Lovgren '505 and/or '230, it would have been apparent that there was no proper basis for a *prima facie* case of obviousness.

**2. The Declarations**

Because the Examiner throughout the prosecution viewed the rejections as if they were set in stone, rather than consider the prior art Lovgren evidence, Applicant submitted substantial proofs. Applicant does not now and never has believed that a *prima facie* case of obviousness has been established. Had the Examiner proceeded properly, she would have realized that there was no *prima facie* case. Even after Applicant submitted additional comparative evidence, the rejection was not reconsidered as it should have been.

Over the course of prosecution, Applicant submitted three (3) separate declarations under Rule 132. The declarations were submitted to address the question of lack of enablement in the part art and/or unexpected results of the now claimed invention.

The Office Actions appeared to either confuse or improperly intermingle the concept of showing "unexpectedness" (which presumably is a shorthand reference to unexpected results or benefits) and enablement. A prior art reference is required to enable that which it is cited for and declarations which address either or both of lack of enablement of the prior art or unexpected benefits cannot be dismissed.

The submitted declarations (Molina declaration, the Johansson declaration and the most recent Molina-Millián declaration) were never properly addressed , that is they were given no weight for reasons which are either not relevant or based on information not of record. They were looked at only for their knockdown value with respect to the rejections of record.

The Office Actions further ignored the fact that the cited prior art did not provide process details to enable one to repeat any of the examples therein. As such, Applicant was unfairly burdened with having to attempt clairvoyance. Applicant chose to make comparisons with closer or cumulative prior art which provided operational detail. See *In re Fouche*, 438 F.2d 1237, 169 USPQ 429, 433 (CCPA, 1971) for the proposition, which is also cited in the MPEP, but the Office Actions continue to ignore the *Fouche* holding and failed to address the issue.

**The Molina Declaration**

The first submitted Declaration by Dr. Molina, Mr. Picornell and Mr. Bravo ("the Molina Declaration") set forth the attempts to reproduce Example 6 of Takeda '797 which used coating techniques other than a fluidized bed coater. This experimental work led to the following conclusion:

> "Therefore, even after correcting the defect of the procedure described in section 1) of example 6 of European Patent Application EP 0 642 797 in relation to the quantity of binder material, this procedure does not yield enteric-coated gastroresistant granules of lansoprazole that are appropriate and acceptable from the pharmaceutical standpoint. Consequently, the use of the above procedure does not yield granules equal or similar to those obtained with the procedure contemplated in Patent Application PCT WO 99/06032, particularly as described in example 1 therein."

Therefore, when enteric-coated gastroresistant benzimidazole granules are made by powder-layering techniques using a centrifugal fluidized coating granulator without a separating layer between the active layer and the enteric coating, it results in granules having stability problems and unacceptable low resistance to gastric fluid. See Paragraph No. 5 of that declaration. If properly considered, this declaration would, at the very least, have alerted the

Examiner that her interpretation of Ohno was in error. The submission not only goes to the question of enablement but also goes to the question of non-obviousness in view of the very art relied upon as a primary reference.

**The Johansson Declaration**

The Johansson declaration used DePui's '771 example 5 but omitted applying the separating layer. The omission of the separating layer resulted in dosage forms which showed rapid (within one hour) degradation of the active ingredient. This rapid degradation was not unexpected because such degradation was foretold by the prior art, specifically Lovgren '505 discussed above. In contrast, the present specification shows that the now claimed products produced by the now claimed process have stability over extended periods.

A comparison of 'WO '624' s Example 1 composition and the amounts of the core, separating layer and enteric coating layer to those of Example 5 of DePui '771, as set forth in the Johansson Declaration, shows that the compositions are substantially identical. Hence, what is believed to be the closest example from WO '624 has effectively been shown to result in a poor and unacceptable product when no separating layer is included. Had this declaration been properly considered, it would have alerted the Examiner to lack of enablement in the cited prior art and have the unobviousness of the now claimed invention.

**The Molina-Millián Declaration**

In the third submitted declaration, Dr. Molina-Millián reported on another comparative test. In this test, the declarant fairly reproduced the first step of Example 11 of WO '624 to obtain enteric coated pellets prior to those pellets being compressed to form tablets. The details of the procedure are set forth in that declaration. The declarant produced enteric coated

pellets of lansoprazole and pantoprazole, both of which are substituted benzimidazoles proton pump inhibitors currently on the market in the U.S. as Prevacid® and Protonix® respectively. As noted in Paragraph 10 of the declaration, in each instance, a core material with a creamy white color was obtained prior to the application of the enteric coating.

Annex 1 attached to that declaration shows, in Figure 1, enteric coated lansoprazole pellets and, in Figure 2, enteric coated pantoprazole pellets each according to Example 11 of WO '624. Figure 3 shows lansoprazole pellets according to Example 1 of the present application. As can be observed from Figures 1 and 2, those pellets produced according to Example 11 of WO '624 rapidly underwent a color change signifying degradation, or lack of stability, of the active ingredient in the respective formulations. Such rapid degradation was to be expected. See EP 0247983 and EP 244380 which are believed to contain the same disclosure as U.S. Patent Nos. 4,853,230 and 4,786,505 (the Lovgren patents) respectively. As can be seen from Figure 3 of Annex 1, pellets produced according to the present invention, remained stable. See Paragraph 15.

It is submitted that taken individually or in their entirety, the declarations establish the non-obviousness of the now claimed subject matter and the lack of enablement by the prior art for that which the Examiner has cited that art.

The Johansson declaration was criticized because Johansson compared example 5 of DePui '771 rather than DePui '184. The Examiner maintained that a showing that DePui '771 was not enabling did not extend to the rejection based on DePui '184. However, the disclosures of both of the DePui references are extremely close and, as repeatedly pointed out, Example 4 of DePui '184 does not provide operational detail for any of the apparatus used in that example. Again, see *In re Fouche*, 169 USPQ 429 at 432 to 433. The main difference between the DePui references is that

DePui '771 is directed to a dosage form of a proton pump inhibitor and a prokinetic agent whereas DePui '184 is directed to a dosage form for a proton pump inhibitor and an NSAID. Based on the written disclosures of each of these respective references, and their lack of detail with respect to conditions of process operation, there is no reason from the prior art to expect a different result if Example 4 were produced but without a separating layer. In both DePui references, the concern is the impact of the tabletting process and the enteric coating submerged in the tablet dosage form. Neither of the DePui references suggest that the prokinetic agent or the NSAID change the results.

Further, the reason the declarant in the Johansson declaration indicated that the degradation of the prior art composition without a separating layer was not a surprise is because the prior art foretold that degradation would result. See Lovgren '505 or Lovgren '230. But, this crucial fact of what was to be expected from the prior art was ignored by the Examiner because she had decided not to consider Lovgren '505 or '230 in any respect unless it supported the rejection. Rather than address the merits, the rejections contained pages of unsupported speculation in an effort to require Applicant to submit even more testing. See *In re Benno*, 226 USPQ 603,688 (where there is no mention of the problem to be solved there is no *prima facie* case to overcome by the submission of evidence).

The presently pending claims clearly recite the presence of an alkaline reacting compound in the aqueous or hydroalcoholic suspension-solution which also contains the active ingredient. As established by the Johansson Declaration, repetition of example 5 of the DePui '771 but without the separating layer results in an inferior product showing immediate degradation as is

indicated by the brown color[10]. Thus, the Examiner's previous position that one could simply follow the DePui '771 examples but omit the separating layer has been shown to be in error. There is no reason set forth in the prior art to expect the results would be any different with any example in either of DePui '771 or '184.

Had Lovgren '505 and '230 been properly considered, it would have been apparent that there was no *prima facie* case of obviousness and thus no need for any proofs by Applicant. Certainly when the proofs were submitted any true reconsideration as required by *Piasecki* would have concluded that the claimed subject matter was not obvious.

**3. Other Errors**

**The Term "Comprising"**

The Final Rejection states that because claims 34 and 36 recite "comprising language" it is not exclusionary. In a telephone interview, the Examiner stated that she raised this issue because of Applicant's argument regarding the number of active ingredients in the DePui dosage form in contrast to the language of the present claims. However, it is clear from the discussion bridging pages 8 and 9 of the specification that "comprising" is being used by the PTO to alter, or unreasonably interpret, the limitations expressly stated in the claims. The record does not contain any case authority or any section of the MPEP which permits the PTO to alter a limitation, or interpret it in a manner inconsistent with the specification or the claim language, because of the use of the transitional phrase "comprising". Claims 34 and 36 as pending indicate that the only active is an anti-ulcer compound.

[10] In contrast, products made by the now claimed process have been approved by the regulatory authority of at least one European country which indicates the product has a suitable stability and product life.

## Claim Construction

For purposes of examination, an Examiner is only permitted to interpret the claims as broadly as is reasonably supported by the specification. There is no mention in the specification of a second active ingredient being present in the claimed pharmaceutical composition. Thus, the Examiner engaged in an interpretation of a claim beyond that which is permitted. Claims 34 and 36 as pending indicate that the only active is an anti-ulcer compound.

## The Word "Optional"

The Final Rejection suggests that because the DePui references use the word "optional" with respect to the separating layer in the dosage form of the DePui references, that such phraseology translates into the disclosure and enablement of omitting a separating layer from any pharmaceutical composition including the pharmaceutical composition resulting from the now claimed process. This is not the scientific fact nor is it a justifiable inference from the disclosure. Neither of the DePui references provides any stability testing data on the DePui composition. The Examiner's only basis for this interpretation was the standard dictionary definition of "optional". However, reliance on dictionary definitions is not favored. See *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ 2d 1321 (Fed. Cir. 2005).

## Inherency

Inherency can only be invoked when an event or condition must result not when it may result. There is nothing in the record that provides a basis for reliance on inherency to support an obviousness rejection. Throughout the prosecution the Examiner relied on inherency to support the obviousness rejections. However, it is well established that it is improper to rely on inherency in an obviousness rejection. See *In re Spormann and Heinke*, 363 F.2d 444, 150 USPQ 449, 452

(CCPA 1966) (... unable to find, however, any indication in the references that such a step would have the effect which applicants sought and found...). Also see *Ex parte Weitzenkorn*, 97 USPQ 76 (POBA 1952). Also, the Johansson declaration shows that inherency cannot be relied upon.

**Enablement**

The Office Action comments regarding what must be shown to demonstrate lack of enablement are also in error. The question of enablement goes to claimed subject matter. Applicant has not claimed a pellet *per se* and none of the primary references claim a pellet *per se*. Applicant has claimed a pharmaceutical composition. Such a form must have long term stability. The enablement issue did not go to the claimed subject matter of the prior art but to the fragments of disclosures relied upon by the Examiner.

**Recital of Benefits**

The suggestion that the claims should now recite how long the dosage form is stable is improper. Such characteristics are not properly recited in a claim. See *Preemption Devices Inc. v. Minnesota Mining & Manufacturing Company,* 732 F.2d 903, 221 USPQ 841, 844 (Fed. Cir. 1984) (advantages...do not properly belong in claims...).

**Discoloration**

Those in the art who are familiar with the substituted benzimidazole proton pump inhibitor compounds know that discoloration is an indication of the degradation of the active ingredient. Reference again is made to the Lovgren '505 patent. The Examiner hypothesized that the source of discoloration is from other than degradation. There is no basis for such conjecture. The Examiner was repeatedly called upon to comply with 37 CFR 1.104(d)(2). However, there never was compliance.

## Scope of the Showing

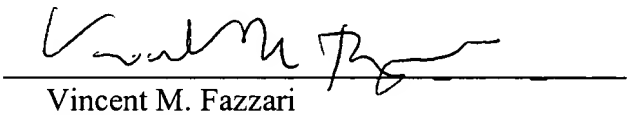
Those of skill in the art familiar with the substituted benzimidazole proton pump inhibitor compounds know that all of the compounds in that group are acid labile and are easily degraded by acid. See the '230 Patent. There was no need for additional examples. Characterizing something as "unclear" with no expressed basis does not require Applicant to submit additional proofs. More than adequate proofs were made. Also, see *In re Benno, supra.*

## CONCLUSION

For the foregoing reasons, it is respectfully submitted that each of the Grounds for Rejection are in error, that appellant's claims are not obvious and are, therefore, patentable over the art of record. Accordingly, the rejections should be reversed and the pending claims should be allowed.

Respectfully submitted,

COHEN, PONTANI, LIEBERMAN & PAVANE LLP

By 

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Dated: December 21, 2007

## CLAIMS[11] APPENDIX

Claim 15: The process of claim 34 further comprising drying the coated charged nucleus.

Claim 16: The process of claim 34, wherein said binder in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of saccharose, starch, methylcellulose, carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), polyvinyl pyrrolidone (PVP), dextrin or gum arabic, either alone or mixed, dissolved in water, ethanol or a mixture of both at 50% (v/v).

Claim 18: The process of claim 34, wherein said surface-active agent present in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of sodium lauryl sulphate, polysorbate, poloxamer or other ionic and non-ionic surface-active agents.

Claim 19: The process of claim 34, wherein said filling material in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of lactose, starch, saccharose and microcrystalline cellulose.

Claim 20: The process of claim 34, wherein said disintegrating-swelling excipient in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of starch, calcium carboxymethyl cellulose (CMCCa), sodium glycolate starch and hydroxypropyl cellulose (L-HPC).

Claim 21: The process of claim 34, wherein said enteric coating polymer in said external gastro-resistant coating is selected from the group consisting of methyl cellulose, hydroxylethyl cellulose (HEC), hydroxylbutyl cellulose (HBC), hydroxypropylmethyl cellulose (HPMC), ethyl cellulose, hydroxymethyl cellulose (HMC), hydroxypropyl cellulose (HPC), polyoxyethylene glycol, castor oil, cellulose phthalic acetate, phthalate of HPMC, succinate acetate of HMC, sodium carboxymethylamylopectin, chitosan, alginic acid, carrageenans, galactomannons, tragacanth, shellac, agar-agar, gum arabic, guar gum, xanthan gum, polyacrylic acids, methacrylics and their salts, polyvinyl alcohol (PVA), polyethylene and

[11] Certain of the claims contain typographical errors which, if the claims are allowed, will be corrected.

polyproprylene oxides and mixtures thereof.

Claim 22: The process of claim 41, wherein said plasticizer in said external gastro-resistant coating is selected from the group consisting of triethyl citrate (TEC), polyethylene glycol (PEG), cetyl alcohol and stearyl alcohol.

Claim 23: The process of claim 34, wherein said surface-active agent in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of sodium lauryl sulphate, polysorbate and poloxamer.

Claim 24: The process of claim 41, wherein said pigment in said external gastro-resistant coating layer is selected from the group consisting of titanium dioxide and iron sesquioxide.

Claim 25: The process of claim 41, wherein said lubricant in said external gastro-resistant coating layer is selected from the group consisting of talc, magnesium stearate and glyceryl mOhnostearate.

Claim 30: The process of claim 34 wherein the filling material is selected from the group consisting of mannitol, sorbitol or gelatin.

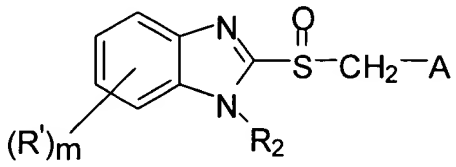
Claim 31: The process of claim 34 wherein the alkaline reacting compound is selected from the group consisting of sodium, potassium, aluminum or calcium acetate; sodium, potassium, aluminum or calcium glycerophosphate; (tris)-hydroxymethylaminemethane (tromethamine); N-methylglucamine, 2-amine-2-methyl-1, 3-propanediol; 2-amine-2-methyl-1propanole; sodium, potassium, magnesium, calcium, aluminum or aluminum hydroxide salts of amino acids, salts derived from organic or weak inorganic acids, bases and basic amino acids.

Claim 33: The process of claim 41 wherein the plasticizer is selected from the group consisting of diethyl phthalate, dibutyl phthalate, dimethyl phthalate, diocytl adipate, dioctyl phthalate, dioctyl terephthalate, butyloctyl phthalate, triethylene glycol di-2-ethylhexanoate, trioctylmethylate, glyceryl triacetate, glyceryl tripropionate and, 2,2,4-trimethyl-1, 3-pentanedioldiisobutyrate.

Claim 34: A process for making an oral pharmaceutical preparation comprising:

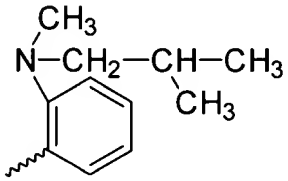
a) coating an inert nucleus to form a substantially non-porous layer thereon by spraying on the nucleus an aqueous or hydroalcoholic suspension-solution, which comprises:

(i) an active ingredient, said active ingredient consisting of a compound having anti-ulcer activity of general formula I:

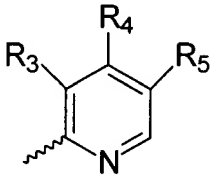


(I)

wherein A is:



or



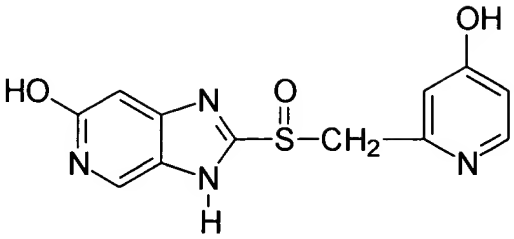
wherein $R^3$ and $R^5$ are the same or different, and may be hydrogen, alkyl, alkoxy, or alkoxyalkoxy;

$R^4$ is hydrogen, alkyl, alkoxy which can be fluorinated, alkoxyalkoxy, or optionally alkoxycycloalkyl;

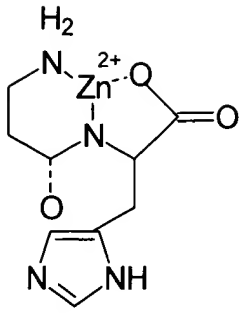
$R^1$ is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl;

$R^2$ is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl; and, m is a whole number from 0 to 4;

or of general formula II or III,



(II)



(III),

(ii) an alkaline reacting compound, and

(iii) at least one pharmaceutically acceptable excipient selected from the group consisting of: a binder, a surface-active agent, a filling material and a disintegrating-swelling excipient;

b) drying the active layer formed during said spraying to form a charged nucleus; and

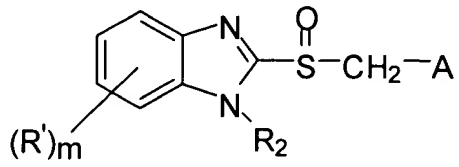
c) coating the charged nucleus by spraying a solution which contains an enteric coating polymer with at least one pharmaceutically acceptable excipient to form a gastro-resistant external coating layer on said charged nucleus

wherein the steps a) to c) are performed in a Wurster-type fluidized bed coater.

Claim 36: A process for making an oral pharmaceutical preparation comprising:

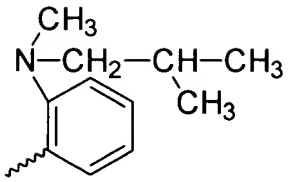
a) coating an inert nucleus in a fluidized bed coater to form a substantially non-porous layer thereon by spraying on the nucleus an aqueous or hydroalcoholic suspension-solution, which comprises:

(i) an active ingredient, said active ingredient consisting of a compound having anti-ulcer activity of general formula I:

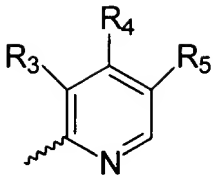


(I)

wherein A is



or



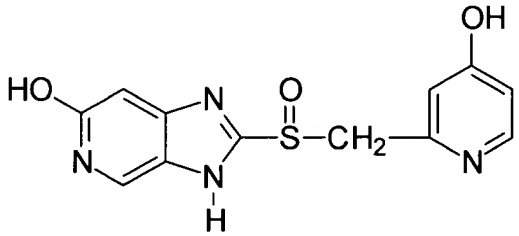
wherein $R^3$ and $R^5$ are the same or different, and may be hydrogen, alkyl, alkoxy, or alkoxyalkoxy;

$R^4$ is hydrogen, alkyl, alkoxy which can be fluorinated, alkoxyalkoxy, or optionally alkoxycycloalkyl;

$R^1$ is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl;

$R^2$ is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, or alkoxycarbonylmethyl alkylsulfonyl; and, m is a whole number from 0 to 4;

or of general formula II or III,



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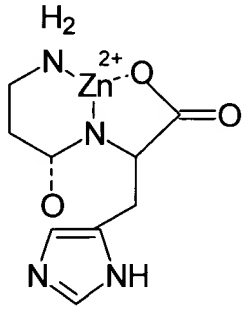


$(III)_1$

(ii) an alkaline reacting compound, and

(iii) at least one pharmaceutically acceptable excipient selected from the group consisting of: a binder, a surface-active agent, a filling material and a disintegrating-swelling excipient;

b) drying the active layer formed during said spraying to form a charged nucleus in said fluid bed coater; and

c) coating the charged nucleus in the fluid bed coater by spraying on said charged nucleus a solution which contains an enteric coating polymer with at least one pharmaceutically acceptable excipient to form an gastro-resistant external coating layer thereon,

wherein the fluidized bed coater is a Wurster-type fluidized bed coater.

Claim 39: The process of claim 34 wherein the oral pharmaceutical preparation is stable.

Claim 40: The process of claim 36 wherein the oral pharmaceutical preparation is stable.

Claim 41: The process of claim 34 wherein the least one pharmaceutically acceptable excipient is at least one of a plasticizer, a surface-active agent, a pigment and a lubricant.

Claim 42: The process of claim 34 wherein the inert nucleus has an initial size between 200 and 1800 micrometers.

Claim 43: The process of claim 42 wherein the inert nucleus has an initial size of 600 to 900 micrometers.

Claim 44: The process of claim 34 wherein the inert nucleus is a neutral spherical microgranule which includes in its composition at least two of: sorbitol, mannitol, saccharose, starch, microcrystalline cellulose, lactose, glucose, trehalose, maltitol or fructose.

Claim 45: The process of claim 36 wherein the least one pharmaceutically acceptable excipient is at least one of a plasticizer, a surface-active agent, a pigment and a lubricant.

Claim 46: The process of claim 34, wherein said alkaline reacting compound in said aqueous or hydroalcoholic solution-suspension is selected from the group consisting of trisodium phosphate, disodium phosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, aluminum hydroxide, carbonate, phosphate or citrate of aluminum, calcium, sodium or potassium, and the mixed compounds of aluminum/magnesium $A1_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$ or $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$ and alkaline reacting amino acids.

Claim 47: The process of claim 31 wherein the hydroxide salts are of amino acids such as lysine, glutamic acid, glycine or pyrimidinecarboxlic acids such as nicotinic acid.

Claim 48: The process of claim 31 wherein the basic amino acids are arginine, histidine, lysine and triptophane.

Claim 49: The process of claim 34 wherein the enteric coating polymer present in the external gastro-resistant coating is selected from the group consisting of phthalate of hydroxypropylmethyl cellulose, succinate acetate of hydroxymethyl cellulose, polyvinyl acetate phthalate, and cellulose acetate trimethylate.

Claim 50: The process of claim 34 wherein the alkaline reacting compound is a salt derived from guanidine

## EVIDENCE APPENDIX

1. U.S. Patent No. 4,786,505
2. U.S. Patent No. 4,853,230
3. Molina Declaration
4. Johansson Declaration
5. Molina Millian Declaration

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Carlos PICORNELL DARDER et al.

Serial No.: 09/491,624

Filed: January 26, 2000

For: Oral Pharmaceutical Preparation Comprising an Antiulcer Activity Compound, and Process for its Production

Examiner: Amy E. Pulliam
Group Art: 1615

# DECLARATION

**DECLARATION in relation to Patent Application PCT WO 99/06032**

The undersigned:

Carlos Picornell Darder, graduate in Pharmacy from the Universidad Complutense de Madrid, with address at Calle Machaquito 48, Madrid 28043,

Carmen Molina Millán, graduate in Chemical Sciences and Pharmacy from the Universidad Complutense de Madrid and doctor in Pharmacy from the Universidad Complutense de Madrid, with address at calle Virgen del Puig nº 9, 8º, 3ª, Madrid 27028, and

Lázaro Bravo Blanco, graduate in Pharmacy from the Universidad Complutense de Madrid, with address at calle Arte 16, 5ºE, Madrid 28033

HEREBY STATE AND SET ON RECORD THE FOLLOWING:

**FIRST**

One of the undersigned, Carlos Picornell, is the person shown as the inventor of Patent Application PCT WO99/06032.

The other two undersigned, Carmen Molina and Lázaro Bravo, are senior specialists in pharmaceutical technology, particularly as it relates to controlled-release dosage forms, and are currently employed by the company Liberación Controlada de Sustancias Activas, S.A. (LICONSA), which company is the present applicant for Patent Application PCT WO99/06032.

**SECOND**

We have performed experimental work to reproduce section 1) of example 6 of European Patent Application EP 0 642 797 and to obtain lansoprazole granules which, according to that document, are obtained by the procedure described. The aim of this work was to compare the resultant lansoprazole granules with those obtained from the procedure object of Patent Application PCT WO99/06032, particularly as described in example 1 of this patent application.

**THIRD**

Section 1) of example 6 of European Patent Application EP 0 642 797 literally discloses the following:

"1) Granules containing lansoprazole was prepared as follows

| Ingredients | mg |
|---|---|
| **Lansoprazole** | **30** |
| **Magnesium Carbonate USP** | **22.4** |
| **Sugar Spheres NF** | **110.0** |
| **Sucrose NF** | **59.8** |
| **Starch NF** | **36.4** |
| **Low-Substituted Hydroxypropyl Cellulose NF (L-HPC-31)** | **40.0** |
| **Hydroxypropyl Cellulose NF (HPC-L)** | **1.4** |
| **Methacrylic Acid Copolymer LD (Eudragit L30D-55) (Röhm Pharma Co.)** | **44.6** |
| **Polyethylene Glycol NF (PEG-6000)** | **4.4** |
| **Titanium Dioxide USP** | **4.4** |
| **Polysorbate 80 NF (Rheodol TW-0120)** | **2.0** |
| **Talc USP** | **14.0** |
| **Colloidal Silicon Dioxide NF (Aerosil)** | **0.6** |
| **Purified water * USP** | **q.s.** |
| Total | 370.0 |

*: Removed during the manufacturing process
USP: The United States Pharmacopeia
NF: The National Formulary

Sugar spheres was coated with a mixture of lansoprazole, magnesium carbonate, sucrose, starch and L-HPC-31 by means of spraying aqueous HPC-L solution in a centrifugal fluid-bed granulator (CF-360S, Freund Co.), and the resultant wet granules were dried in a vacuum oven at about 40° C for about 18 hours, and then sieved. The obtained granules were coated with aqueous enteric Eudragit suspension containing PEG-6000, talc, titanium dioxide and Rheodol TW-0120 in a fluid-bed coater (FD-Coater FLO-60, Freund Co.), and sieved, and then dried in a vacuum oven at about 42° C for about 18 hours. The obtained granules were mixed with talc and Aerosil."

This description omits a significant amount of data and parameters needed to use the procedure described, specifically omitting information on the following aspects related to the granulation step:

- Size of the sugar spheres comprising the core
- Concentration of the aqueous HPC-L solution to be sprayed
- Particle sizes of the solid excipients
- Conditions for introducing the solid mixture of active ingredient and excipients (pressure and rate of introduction) into the granulator
- Conditions for spraying the HPC-L binder solution (pressure and rate of spraying)
- Process temperature and volume of air

Moreover, in the complete text of European Patent Application EP 0 642 797 we have been unable to locate additional information or references that would allow the omitted data and parameters to be completed.

In view of this situation, we have attempted to supply the omitted data by applying our expertise in the field, endeavouring to maintain the essential aspects of the description without applying any inventive step that would alter the description contained in the document involved.

**FOURTH**

Using an MP-1-Roto Processor centrifugal fluid-bed granulator from the NIRO firm, we have performed pilot tests with the following amounts of starting materials:

| | |
|---|---|
| Sugar spheres (cores of 500-600µm) | 600 g |
| Lansoprazole | 163.6 g |
| Magnesium carbonate | 122 g |
| Sucrose | 326 g |
| Starch | 198.6 g |
| L-HPC-31 | 218.2 g |
| HPC-L (binder) | 7.6 g |

that maintain the weighted proportions described in example 6 of European Patent Application EP 0 642 797.

Since the envisaged amount of HPC-L binder is very small, it was used in the form of an aqueous solution of 5% by weight (151 g of solution), which represents the dilution allowing the largest amount of water while maintaining the binder capacity of the HPC-L. As a result, we attempted to make available sufficient water to complete the process of active coating of the inert sugar spheres.

The volume of air that allows the 600 g of sugar spheres to be kept in motion is 70-80 $m^3/h$.

The solid mixture is introduced at a pressure of 0.5 bar, allowing an introduction rate of 25 g/minute.

The spray rate of the 5% aqueous solution of HPC-L binder is at least 10-11 g/minute, which allows problem-free operation of the peristaltic pump at a spray pressure of 1 bar.

The process temperature is set at 30-35 °C.

Based on the stated introduction rate of the solid mixture (25 g minute) and the total weight of this mixture (1028 g), the process takes at least 41 minutes. Nevertheless, some 15 minutes are needed to spray 151 g of 5% aqueous solution of HPC-L binder material at the required minimum spray rate (10 g/minute).

In order to make the solid mixture introduction time and the solution spraying time the same, the aqueous solution of binder material would have to be diluted still further . However, this is not possible since the binding capacity of the HPC-L decreases when the dilution is increased.

We consider that, as described in example 6 of European Patent Application EP 0 642 797, the weighted ratio of 1028:7.6 between the solid mixture and HPC-L binder material is too high for the process to be effective.

This aspect is critical, as confirmed by tests we have conducted that yield completely inappropriate results in which more than half the solid mixture has still not been loaded in the centrifugal granulator by the time the binder solution has been entirely sprayed. Moreover, the equipment was left with too much powder not adhered to the granules.

Therefore, as it is described in section 1) of example 6 of European Patent Application EP 0 642 797, the procedure in question does not yield lansoprazole granules suitable for subsequent enteric coating. Consequently, the use of the above procedure does not produce granules equal or similar to those obtained by the procedure object of Patent Application PCT WO 99/06032, particularly as described in example 1 therein.

**FIFTH**

Based on what we have stated in the fourth point, in order to ensure a sufficient amount of aqueous solution of binder material to complete the introduction of the solid mixture, we repeated the experiment with all the same parameters except for the amount of 5% HPC-L binder material, which was increased more than three-fold. In other words, we employed 485 g of 5% HPC-L solution, which represents an overage of 319% with respect to the HPC-L amount indicated in example 6 of European Patent Application EP 0 642 797.

Once the granulation step was completed and before proceeding to the enteric coating step, the following was observed:

(a) The process yield was only 85% because part of the solid mixture did not adhere to the granules. Consequently, powder remained on the equipment walls.

(b) The resultant granules were screened in cascade to between 700 and 125 microns, and it was observed that 18% of the particles had sizes below 600 microns and were inappropriate, while 81.3% had a particle size above 600 microns.

(c) Observation of the particles under an optical microscope revealed that the particles were not spherical and that roundness values were far from one. Only 1% of the particles had a roundness value between 1.05 and 1.1, while 26.47% had values between 1.10 and 1.15 and the rest had values above 1.15, sometimes being as high as 1.5.

(d) The particle appearance was highly irregular, being glassy on occasion, leading us to believe that these cases consisted in remains of solid mixture not adhered to the granules.

(e) The granules were excessively fragile, producing considerable amounts of dust when handling the bags that contain the granules (low mechanical strength).

We used the resultant granules to perform the coating step in an Aeromatic Fielder MP-4-RP-F2 Multi-processor from the NIRO company, in accordance with the data and parameters described in example 6 of European Patent Application EP 0 642 797.

Despite working with volumes of air around 250 $m^3/h$, the fragility of the resultant granules meant that the granules broke in significant proportions, causing the equipment to be heavily coated with dust.

Because the granules broke, lansoprazole came into contact with the enteric coating polymer (Eudragit). This interaction resulted in degradation of the active ingredient as seen by the formation of a dark brown colouring.

In order to minimise degradation of the active ingredient, a slow spray rate of around 10 g/minute was used to minimise excess moisture that would favour interaction between lansoprazole and the Eudragit polymer.

Nevertheless, the resultant coated granules had an intense dark brown colouring that indicated significant degradation of the active ingredient.

When the resultant coated granules were tested to determine the resistance to gastric fluid as described in the European Pharmacopoeia and USP-25, a value of 9.3% was obtained. This is an unacceptably low value, since the amount of active ingredient remaining in the dosage form after the gastro-resistance test would be expected to be no less than 90% of the label amount.

HPLC assay of the lansoprazole content of the resultant coated granules showed a value of 75 mg/g, an unacceptable deviation with respect to the theoretical amount (99 mg/g).

Therefore, even after correcting the defect of the procedure described in section 1) of example 6 of European Patent Application EP 0 642 797 in relation to the quantity of binder material, this procedure does not yield enteric-coated gastroresistant granules of lansoprazole that are appropriate and acceptable from the pharmaceutical standpoint. Consequently, the use of the above procedure does not yield granules equal or similar to those obtained with the procedure contemplated in Patent Application PCT WO 99/06032, particularly as described in example 1 therein.

**SIXTH**

We have performed the experimental tests mentioned in this declaration of good faith, applying our expertise and experience as experts in pharmaceutical technology in a way that we sincerely believe to be correct.

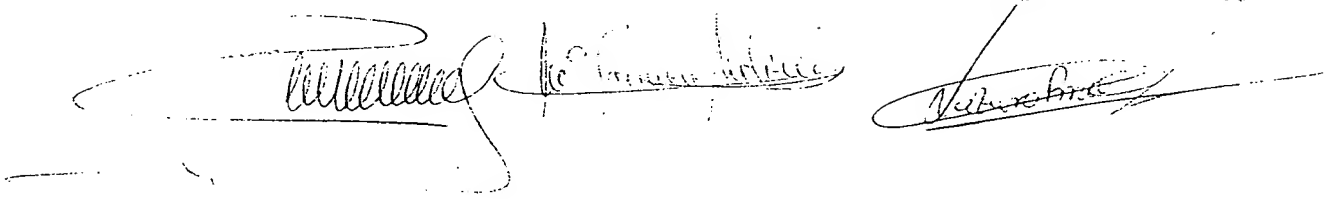
As a result, we expressly state that the conclusions we have reached correspond to reality and we are convinced that they are correct.

That all the statements made herein of their own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that wilful false statements may jeopardise the validity of Application Serial No. 09/491624 or any patent issuing thereon.

Madrid, 4th October 2002.

Signed

Carlos Picornell Darder  Carmen Molina Millán  Lázaro Bravo Blanco



Attorney Docket # 4948-2PCRCE2

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**



In re Application of

Carlos PICORNELL DARDER et al.

Serial No.: 09/491,624

Filed: January 26, 2000

For: Oral Pharmaceutical Preparation Comprising an Antiulcer Activity Compound, and Process for its Production

Examiner: Sharmila S. Gollamudi
Group Art: 1615

Mail Stop **Amendments - Fees Due**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**DECLARATION OF MONA JOHANSSON UNDER RULE 132**

## Declaration related to US 6,132,771 to Depui et al.

**The undersigned, Mona Johansson declares as follows:**

1. I am an employee of LICONSA and an expert in the field of pharmaceutical technology, especially in the area of pellets formulations. I am graduated in Chemical Engineering by the Lulea University of Technology and I work at LICONSA S.A. in the development department. I have worked with pellets formulations at LICONSA and at another company since 1999.

2. I have been asked to fairly reproduce the first step of the example 5 of US patent n° 6.132.771 to Depui et al. to obtain enteric coated pellets but without the separating layer before proceeding to compress them to obtain tablets (second step of Example 5).

3. Regarding the process for obtaining coated pellets (not the tablets) the Example 5 of US 6.132.771 read as follows:

> **Example 5**
>
> Multiple unit dosage form comprising lanzoprazole and mosapride (batch size 500 tablets).
>
> Core material
>
> | | |
> |---|---|
> | Lanzoprazole | 400 g |
> | Sugar sphere seeds | 400 g |
> | Hydroxypropyl methylcellulose | 80 g |
> | Sodium laurylsulfate | 3 g |
> | Water purified | 1500 g |
>
> Separating layer
>
> | | |
> |---|---|
> | Core material (acc. to above) | 400 g |
> | Hydroxypropyl cellulose | 40 g |
> | Talc | 69 g |
> | Magnesium stearate | 6 g |
> | Water purified | 800 g |
>
> Enteric coating layer
>
> | | |
> |---|---|
> | Pellets covered with a separating layer (acc. to above) | 400 g |
> | Methacrylic acid copolymer (30)% suspension) | 667 g |
> | Triethyl citrate | 60 g |
> | Mono- and diglycerides (NF) | 10 g |
> | Polysorbate 80 | 1 g |
> | Water purified | 420 g |
>
> Suspension layering was performed in a fluid bed apparatus. Lansoprazole was sprayed onto the sugar sphere seeds from a suspension containing the dissolved binder in a water solution. Pellets covered with separating layer and enteric coating layer were produced as in example 1.

Regarding the covering process with separating layer and enteric coating layer, Example 1 reads as follows:

> The prepared core material was covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with a hydroxypropyl methylcellulose solution containing magnesium stearate. The overcoating layered pellets were classified by sieving.

Since in the Example 5 a procedure for producing both the intermediate layer and the enteric coating layer is not explicitly described, I have assumed that said procedure should be also similar to those described in Example 1 without the step of forming the inert separating layer.

As observed, from an experimental point of view, Examples 1 and 5 lack many technical details, which I have completed following my best professional knowledge.

To produce both first coating and enteric coating I have used a standard bottom spray fluidized bed apparatus (model HKC-5) ), and usual working conditions. The coating of the active layer was performed with an air flow of 320-340 $m^3$/hour, atomizing pressure 1.4 bars and a product temperature of 38° C. The coating flow was approximately 26 g/min. The process for application of the enteric coating layer was performed in similar conditions, but with a lower coating flow, approximately 20 g/min to avoid agglomeration.

As the methacrylic acid copolymer I have used Eudragit L30 D55 , which is a standard methacrylic acid copolymer for enteric coatings and it is the same copolymer used in the Example 1 of the patent application under examination.

There are many types of "mono- and diglycerides" and the Example 5 is silent on this. I have selected glyceryl monoestearate 40-55 as glidant in the enteric coating, which according to the Handbook of Pharmaceutical Excipients, Fourth Edition, page 264 (ISBN-0853694729) contains at least 40% of monoglycerides and 30-45% of diglycerides.

For a good working of the fluidized bed apparatus used, which is a 5 litres apparatus, it is necessary having higher quantities of materials than those explicitly described in the Examples. Accordingly, I have increased the amounts of the different components, but maintaining the same proportions of Example 5 and the sugar spheres had a weight of 2 kg.

The rest of details not mentioned above literally corresponds to the specifications of Examples 1 and 5.

4. The process of the first coating layer (active substance layer) was successful and performed without problem. The core materials obtained before adding the enteric coating layer had a white-creamy colour.

5. Nevertheless, important problems rose when I proceed to apply the enteric coating layer of Example 5 due to pellet's tendency to agglomerate. Even though the flow rate was decreased, agglomerate was formed. In addition, the pellets got a brownish colour already after 1 hour of coating.

Figure 1 of Annex 1 shows the evolution of the colour of the pellets obtained when reproducing example 5 of US 6.132.771 without the separating layer.

Lansoprazole pellets (core material of Example 5)

- Sample A pellets with the core material according to Example 5 of US 6.132.771, before starting to spray the enteric coating

- Sample B pellets after complete spraying of the enteric coating according to Example 5 of US 6.132.771 but without the separating layer

6. The yellowish brown colour of the obtained pellets show a degradation of the active matter and said pellets are completely unacceptable in pharmaceutical compositions.

7. The results obtained in working Example 5 of US 6.132.771 where not a surprise for me, because the prior art, for instance EP0247983 (US 4,786,505) and EP244380_(US 4,853,230) cited in the patent application, taught that an inert separating layer should be placed between the core material and the outer enteric coating layer to avoid the contact between the anti-ulcer benzimidazole compound (omeprazole, lansoprazole, pantoprazole, etc.) and the acidic component (methacrylic copolymer) of the enteric layer. Is it also mentioned that benzimidazole compounds are not stable in acidic medium, and in contact with acidic compounds they suffer degradation and develop a strong colour.

In comparison, Figure 2 of Annex 1 shows the evolution of the colour during the enteric coating process of lansoprazole pellets prepared according the Example 1 of the patent application under examination.

Lansoprazole pellets (Example 1 of the patent application under examination)

- Sample C pellets with core material prepared according to Example 1 of the patent application under examination, before starting to spray the enteric coating

- Sample D pellets after complete spraying of the enteric coating according to Example 1 of the present application under examination

The pellets obtained according to said Example 1, even not having an inert separating layer, maintained a stable white-creamy colour during the full process and, according to the data showed in Example 1, are stable during storage for several months, even at high temperature and humidity.

8. Finally, Figure 3 of Annex 1 shows the difference in colour between the final pellets obtained when reproducing example 5 of US 6.132.771 without the separating layer (Sample B) and the final pellets made according to Example 1 of the present application under examination (Sample D).

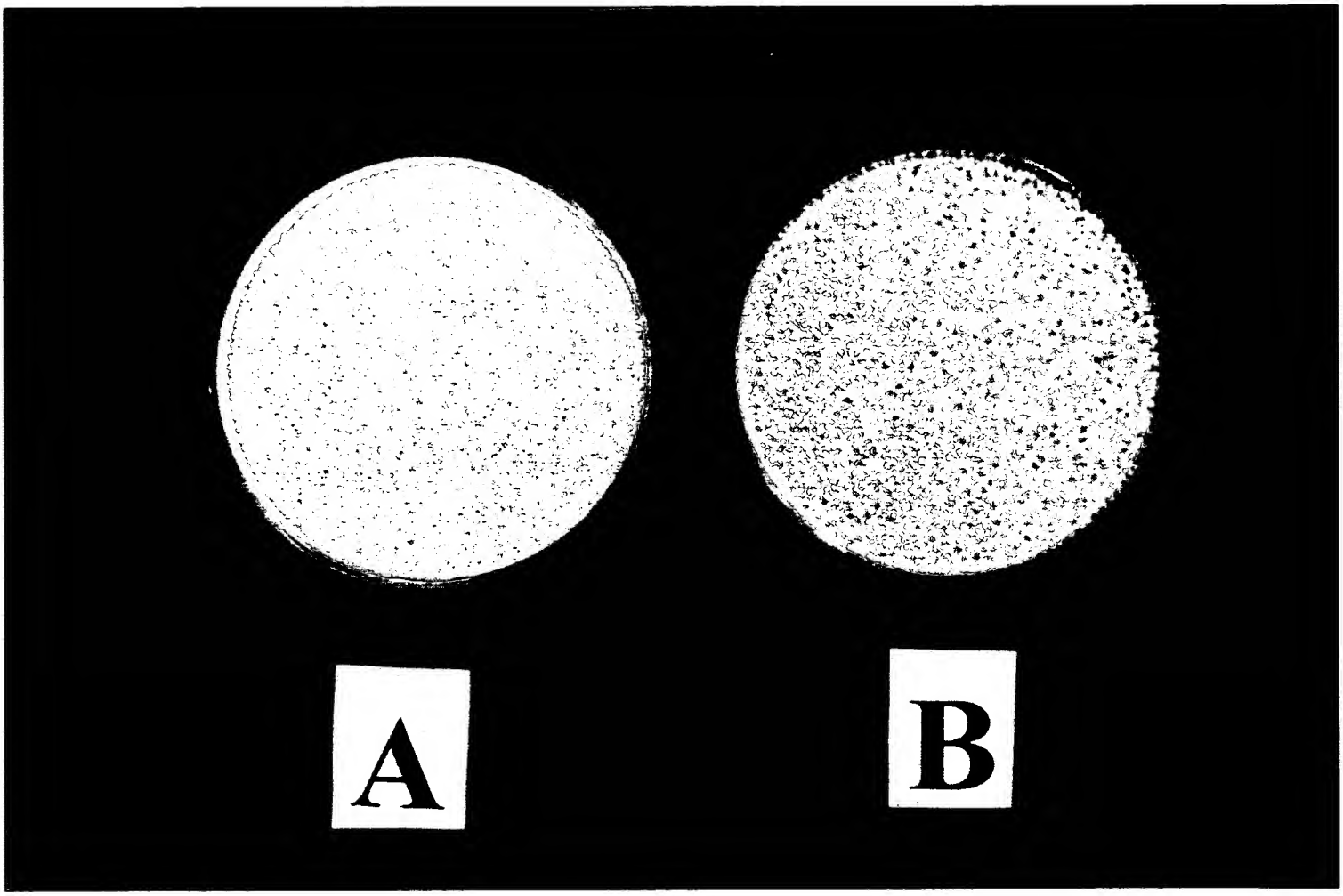
9. In my opinion the obtained results show that Example 5 of US 6,132,771 does not allow preparing the oral pharmaceutical preparations claimed in the patent application. In fact, it is my conviction that working said example 5 does not allow obtaining any acceptable lansoprazole pharmaceutical composition, due to the high colour developed as a consequence of the acidic degradation of the active compound.

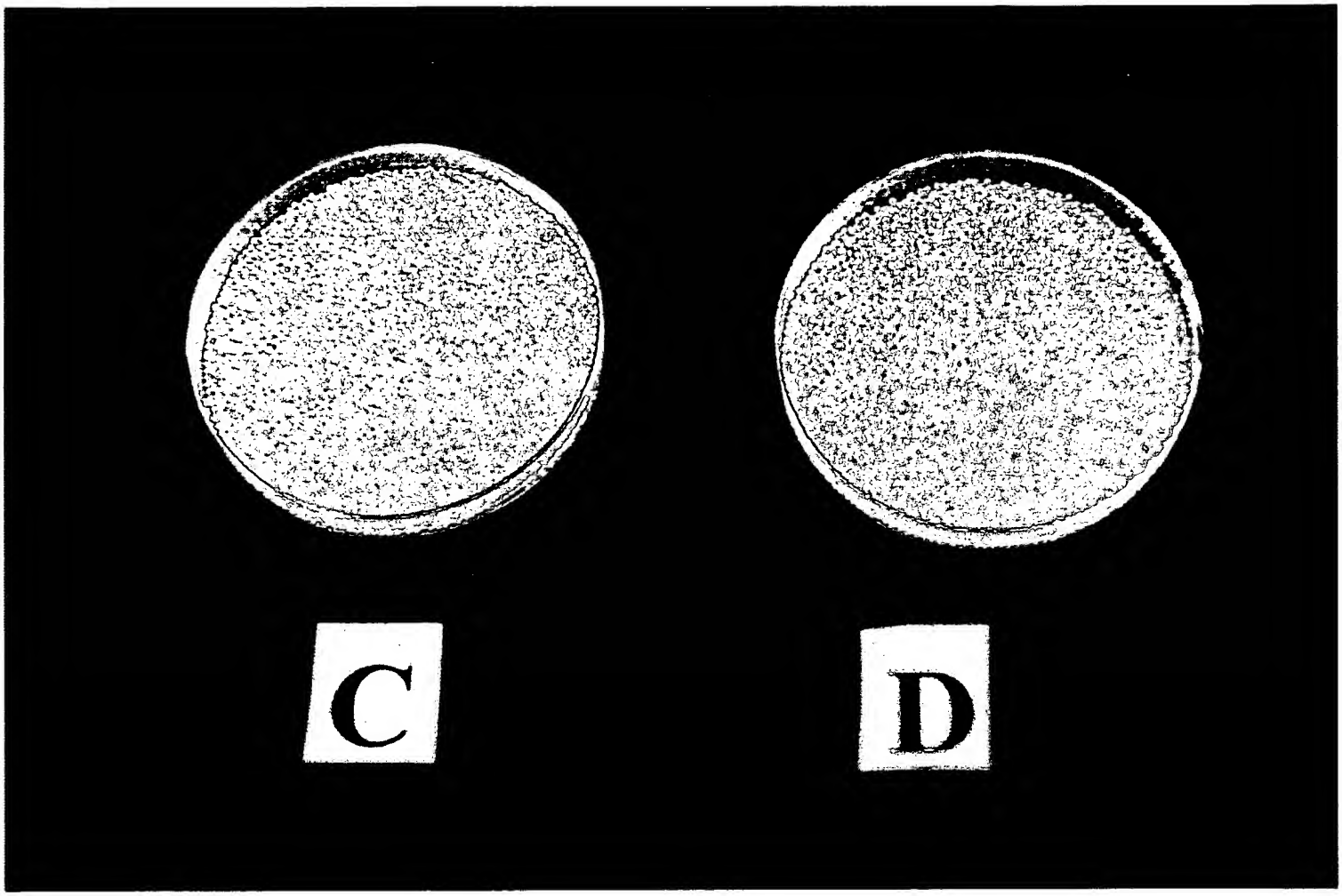
10. All the statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of Application Serial No. 09/491,624 or any patent issuing thereon.

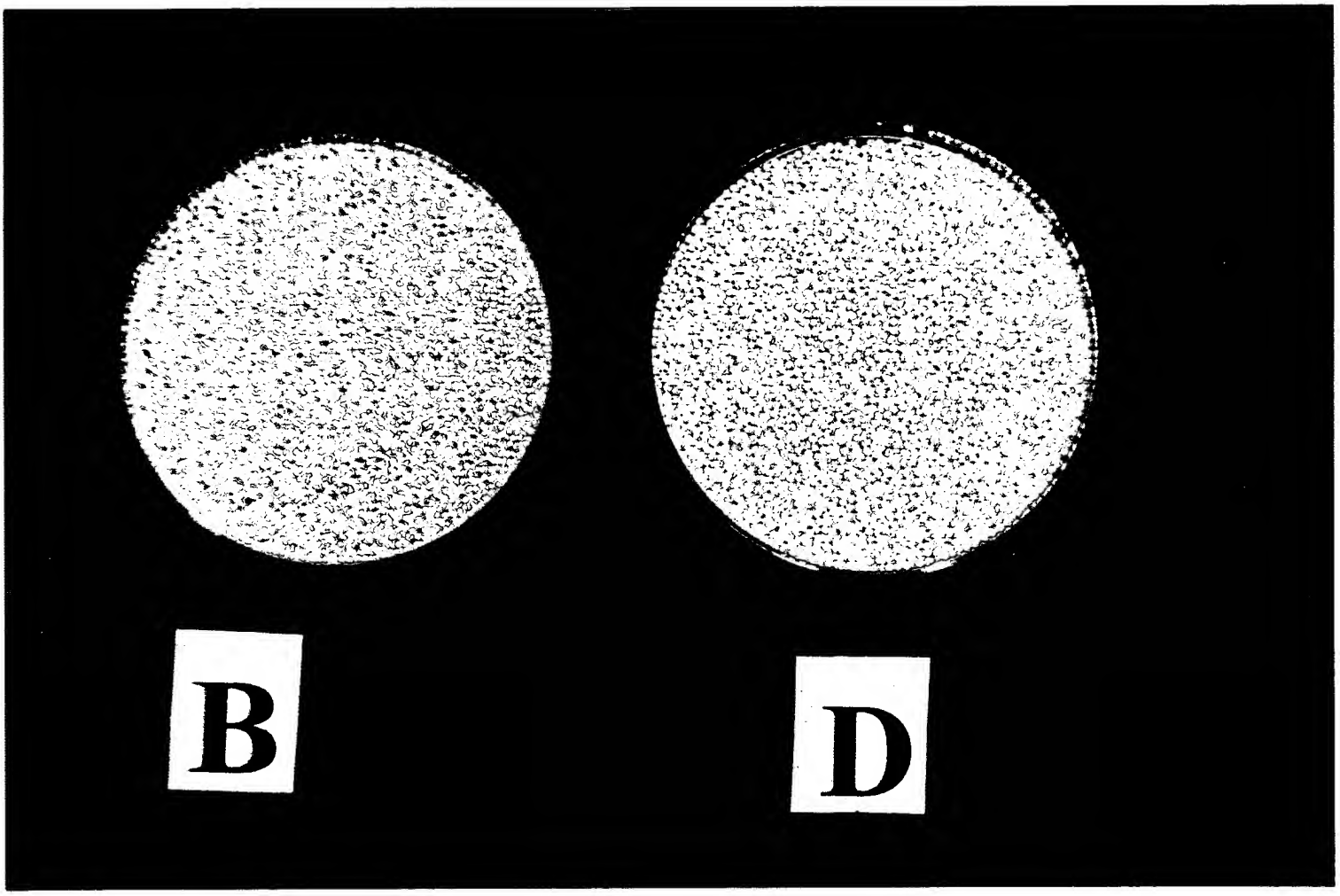
Date: 29 august 2005

Signature:

Mona Johanson
M.Sc. Chem. Eng.


A
B


C
D


B
D

Attorney Docket # 4948-2PCRCE3 PATENT



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of
Carlos PICORNELL DARDER
Serial No.: 09/491,624
Filed: January 26, 2000
For: Oral Pharmaceutical Preparation Comprising an Antiulcer Activity Compound, and Process for its Production

Examiner: Sharmila S. Gollamudi
Group Art: 1616

Mail Stop Non Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**DECLARATION OF DR. CARMEN MOLINA-MILLÁN**

SIR:

The undersigned, Dr. Carmen Molina Millán declares as follows:

1. I am an employee of LICONSA and an expert in the field of pharmaceutical technology. I am a graduate in Chemical Sciences and hold a Ph.D. in Pharmacy from the University of Madrid (Universidad Complutense de Madrid).

2. I am the same Dr. Carmen Molina-Millán who previously submitted a declaration in this matter.

3. I have been asked to fairly reproduce the first step of Example 11 of PCT patent application WO 96/01624 ("WO '624") to obtain the enteric coating layered pellets before these pellets are compressed to form tablets (second step of Example 11).

Suspension layering is performed in a fluid bed apparatus. Pantoprazole is sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder.

5. Since Example 11 does not explicitly describe a procedure for producing the enteric coating layer. I have assumed that the procedure should be similar to those procedures described in Examples 1 and 10 of WO '624, but without the step of forming the inert separating layer.

6. As observed, from an experimental point of view, Examples 1, 10 and 11 lack many technical details, which I have completed following my best professional knowledge. To produce both the first coating and the enteric coating I employed a standard bottom spray fluidized bed apparatus (model HKC5), and usual operating conditions: air volume of 320-340 $m^3$/hour; pressure 1.0-1.2 bar; product temperature 38°C. As the methacrylic acid copolymer I have used Eudragit L30 D55, which is a standard methacrylic acid copolymer used for enteric coatings and the same copolymer used in Example 1 of the presently pending patent application under examination. Serial No. 09/491,624.

7. There are many types of "mono- and diglycerides". Example 11 fails to identify which was used. I have selected glyceryl monoestearate 40-55, which according to the Handbook of Pharmaceutical Excipients, Fourth Edition, page 264 (ISBN-0853694729) contains at least a 40% of monoglycerides and 30-45% of diglycerides.

8. The amount of Polysorbate 80 specified in Example 11 is not enough to completely dissolve or disperse the selected mono-diglyceride (Polysorbate 80 acts as a non-ionic surfactant for dispersing oils in water), and therefore I have increased the amount of Polysorbate 80 until reaching a good solution/dispersion of the mono-diglyceride.

9. For a proper operation of the fluidized bed apparatus used, it is necessary to employ larger quantities of materials than those explicitly described in the Examples. Accordingly, I have increased the amounts of the different components, but maintained the same proportions of the components of Examples 1, 10 and 11 (except in the case of the Polysorbate 80 for the reasons that I have explained above). The remainder of the details not mentioned above literally correspond to the specifications set forth in Examples 1, 10 and 11 of WO '624.

10. I obtained a "core material" according to each of Examples 1 and 10 without having significant problems. Both core materials had a white-creamy color prior to the application of the enteric coating layer.

11. However, serious problems were encountered when I proceeded to apply the enteric coating layer of Example 11. The rate of spraying of the enteric coating solution/dispersion had to be slower than usual (at about 6-8 g/minute) because the pellets showed an increasing tendency to stick. Also, the pellets began to exhibit a brown color which became darker with time.

12. Figures 1 and 2 of Annex 1 hereto show the evolution of the color of the pellets during the enteric coating process:

Lansoprazole pellets (core material of Example 1)

Sample A - pellets prior to application of the enteric coating.
Sample B - pellets after 1 hour of spraying of the enteric coating.
Sample C - pellets after 2 hours of spraying of the enteric coating.
Sample D - pellets after 5 hours of spraying of the enteric coating.

Pantoprazole pellets (core material of Example 10)

Sample E - pellets prior to application of the enteric coating.
Sample F - pellets after 2 hours of spraying of the enteric coating.
Sample G - pellets after 4 hours of spraying of the enteric coating.
Sample H - pellets after 6 hours of spraying of the enteric coating.

16. In my opinion, the obtained results show that Example 11 of WO '624 does not enable one to prepare the oral pharmaceutical preparations claimed in the presently pending patent application. In fact, it is my conviction that the disclosure of WO '624, including Example 11, does not enable one to obtain any acceptable lansoprazole or pantaprazole oral pharmaceutical composition, due to the strong color developed as a consequence of the rapid acidic degradation of the active compound.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: July 6, 2006

Dr. Carmen Molina-Millán

# ANNEX 1

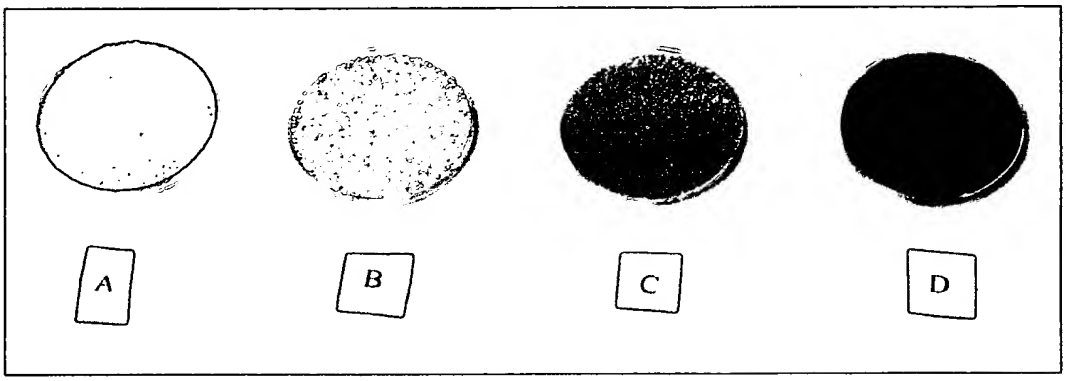



Figure 1: Lansoprazole pellets according to Example 11 of D3

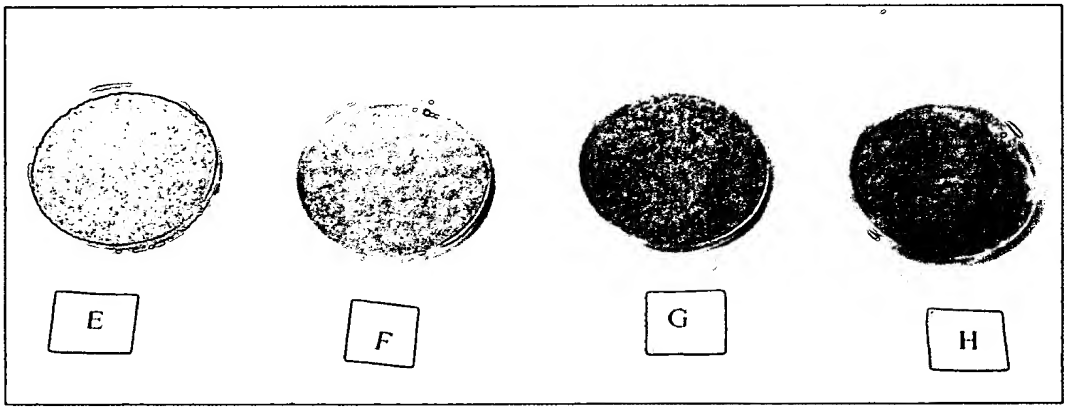



Figure 2: Pantoprazole pellets according to Example 11 of D3

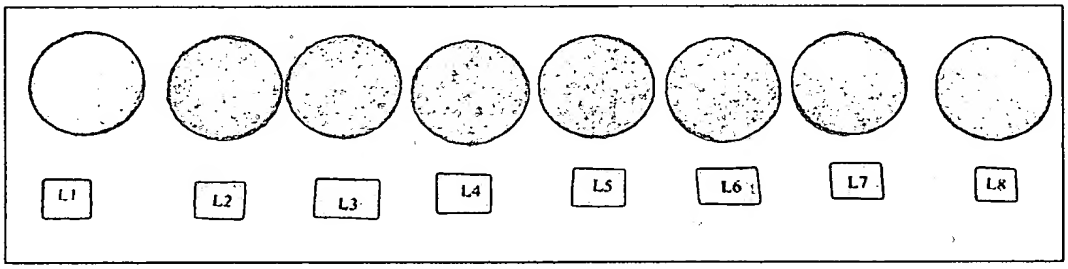



Figure 3: Lansoprazole pellets according to Example 1 of the patent application under examination